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10/668,601	09/24/2003	Aviv Shaish	25727	1529

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,601	SHAISH ET AL.	
	Examiner	Art Unit	
	Michele C. Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The attempt to incorporate subject matter into this application by reference to the non-patent literature references and U.S. patents, on page 1, lines 9-22, is improper because information submitted for consideration must be filed as an information disclosurement statement.

The use of the trademark AVANDIA™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that each letter of the trademark be capitalized or include a proper trademark symbol, such as ™ or ®.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 17 recite the phrase "wherein said algae is *Dunaliella bardawil*". The verb does not agree with its subject in number. Applicant may overcome the rejection by replacing "algae" with alga.

Claims 7 and 15 are rendered vague and indefinite by the trademark term "AVANDIA™". The relationship between a trademark and the product it identifies is often indefinite, uncertain, and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. Arbitrary trademarks which are liable to mean different things at the pleasure of manufacturers do not constitute such language. Ex Parte Kattwinkle, 12 USPQ 11 (Bd. App. 1931). It is suggested that each letter of the trademark be capitalized or include a proper trademark symbol, such as ™ or ®; and, that it is accompanied by the generic terminology.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Levy et al. (U).

Applicant claims a method for treating a disease selected from diabetes mellitus and atherosclerosis comprising administrating to a subject an effective amount of crude *Dunaliella* powder. Applicant claims the method according to Claim 1, wherein said crude *Dunaliella* powder is administered orally. Applicant further claims the method according to Claim 1, wherein said algae is *Dunaliella bardawil*. Applicant further claims the method according to Claim 1, wherein said powder is encapsulated.

Levy teaches a method of treating patients suffering from diabetes mellitus and at high risk of developing atherosclerosis comprising administering an effective amount of an extract obtained from *Dunaliella bardawil* in encapsulated form. Levy teaches that the administration of the algal extract inhibited the oxidation of LDL derived from diabetic patients.

The reference anticipates the claimed subject matter.

Claims 2, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi et al. (V).

Applicant claims a method for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of a subject comprising administrating to the subject an effective amount of crude *Dunaliella* powder. Applicant claims the method according to Claim 2, wherein said crude *Dunaliella* powder is administered orally. Applicant further claims the method according to Claim 2, wherein said alga is *Dunaliella bardawil*.

Takahashi teaches that the administration of an effective amount of a powdered extract of *Dunaliella bardawil* to hypercholesterolemic mice significantly decreased the levels of plasma total cholesterol and LDL-cholesterol.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) and Levy et al. (W).

Applicant's claimed invention was set forth above.

The teachings of Levy (U) were set forth above. Levy does not expressly teach a method of treating a disease wherein the disease is atherosclerosis. However, it would have been obvious to one ordinary skill in the art at the time the invention was made to use the method taught by Levy to provide the claimed invention because at the time the invention was made it was well known in the art of medicine that atherogenesis involves oxidative modification of low-density lipoprotein and that accelerated atherosclerosis is common in patients with diabetes mellitus, as evidenced by the teachings of Levy (U) set forth above; and, that atherogenesis involves oxidative modification of low-density lipoprotein (LDL), as evidenced by the teachings of Levy (W). Firstly, Levy (U) teaches orally administering 60 mg/day of a beta-carotene containing extract of *Dunaliella bardawil* to diabetic patients affected a significant reduction in LDL susceptibility to oxidation, as exhibited by increased lag time and reduction in malondialdehye (MDA) and lipid peroxides (PD). Secondly, Levy (W) teaches a method for reducing the susceptibility of LDL to lipid peroxidation comprising orally administering an effective amount of an extract derived from *Dunaliella bardawil* to healthy patients. For example, Levy (V) teaches that ingestion of a stereoisomeric mixture of 9-cis and all-trans beta-carotene derived from the alga *Dunaliella bardawil* caused a 1.8-fold carotene elevation

in plasma and that oxidation modification of LDL, measured for both dosage intakes, was reduced. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to use the method for treating diabetes taught by Levy (U) to provide a method for treating atherosclerosis because Levy (U) teaches, "Increased susceptibility to oxidation of LDDL derived from patients with diabetes mellitus is associated with abnormal LDL lipid composition and antioxidant content. Natural beta-carotene dietary supplementation normalizes the enhanced LDL oxidation and consequently may be of importance in delaying accelerated development of atherosclerosis in these patients", and, Levy (W) suggests, "Supplementation of beta-carotene may be an important approach to reducing atherosclerosis via its inhibitory effect on the formation of atherogenic oxidized LDL." Thus, as each of Levy (U) and Levy (W) teach that the oral administration of effective amounts of an extract derived from *Dunaliella bardawil* to a either a diabetic patient or a healthy patient have the beneficial functional inhibitory effect on the susceptibility of LDL to oxidative modification, one of ordinary skill in the art would have been further motivated and one would have had a reasonable expectation of success to modify the referenced methods by adjusting the dose amounts of the referenced extracts to provide a method for treating atherosclerosis because Levy (U) teaches that dietary supplementation of a natural isomer mixture of beta-carotene derived from an extract of *Dunaliella bardawil* delays oxidation of LDL derived from patients with mellitus; and, Levy (W) similarly teaches that dietary supplementation of the same algal extract taught by Levy (U) delays oxidation of LDL in healthy patients and

"Atherogenesis involves oxidative modification of low-density lipoprotein (LDL), which is associated with the depletion of the LDL endogenous oxidants."

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed method of treatment are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1 and 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) in view of Beck (A), Pan et al. (B), Heyman et al. (D) and Smith (N).

Applicant's claimed invention of Claims 1 and 8-10 was set forth above. Applicant further claims a method according to claim 1, wherein said crude *Dunaliella* powder is administered together with one or more activators of nuclear receptors. Applicant further claims the method of claim 3, wherein the activators of nuclear receptors are peroxisome proliferator-activated receptor α or γ (PPARα or PPARγ) agonists. Applicant further claims the method according to claim 4, wherein the PPARα or PPARγ agonists are selected from fibrates and thiazolidinediones. Applicant further claims the method according to Claim 5, wherein the fibrates are selected from clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and gemfibrozil. Applicant further claims the method according to Claim 5, wherein the thiazolidinediones are

selected from AVANDIA™, troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone and rosiglitazone.

The teachings of Levy are set forth above. Levy teaches the claimed method for treating diabetes mellitus except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add either fibrates, thiazolidinediones or a combination thereof to the method of treating diabetes mellitus taught by Levy to provide the instantly claimed method of disease treatment because at the time the invention was made the instantly claimed ingredients were known in the art for their beneficial functional effect to treat diabetes mellitus. Firstly, Beck teaches a method for the treatment of normolipidaemic diabetes mellitus comprising orally administering an effective amount of bezafibrate. Secondly, Pan teaches a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, *e.g.*, fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58. For example, in Column 15, line 58 to Column 16, line 2, Pan teaches administering gemfibrozil capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus. Thirdly, Heyman teaches a method of treating diabetes mellitus comprising administering an effective amount of a thiazolidinedione, *e.g.*, troglitazone, BRL 49653 , pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. Fourthly, Smith teaches a method of treating diabetes mellitus comprising administering rosiglitazone. At the time the

invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus taught by Levy to provide the claimed method of treatment because Beck teaches that the oral administration of bezafibrate reduces the insulin level in normolipidaemic patients suffering from diabetes mellitus; Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 27-34; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, *i.e.,* a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ; and, Smith teaches that his method for treating diabetes mellitus comprising administering rosiglitazone provides a beneficial effect on glycaemic control, on page 1, lines 19-22.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the

components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) and Levy et al. (W) in view of Pan et al. (B), Craig et al. (P) and Druzgala et al. (E).

Applicant's claimed invention was set forth above.

The combined teachings of Levy (U) and Levy (W) were set forth above. The combined teachings of Levy (U) and Levy (W) teach the claimed method for treating diabetes mellitus except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add either fibrates, thiazolidinediones or a combination thereof to the method of treating diabetes mellitus and atherosclerosis taught by the combined teachings of Levy (U and W) to provide the instantly claimed

method of disease treatment because at the time the invention was made the instantly claimed ingredients were known in the art for their beneficial functional effect to treat disease conditions such as the claim-designated disease conditions, evidenced by the teachings of Pan, Craig and Druzgala. Firstly, Pan teaches a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, *e.g.*, fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58. For example, in Column 15, line 58 to Column 16, line 2, Pan teaches administering gemfibrozil capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus. In Column 4, lines 27-34, Pan further teaches that the ingredients of his invention prevent the onset of coronary artery disease and prevent the onset of atherosclerosis in mammalian species. Secondly, Craig teaches a method of treating diabetes mellitus and diabetes mellitus related disease conditions, *e.g.,* atherosclerosis, comprising administering rosiglitazone. Thirdly, Druzgala teaches methods of treating disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the administration of a therapeutically effective amount of a thiazaolidinedione, *i.e.,* troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus taught by the combined teachings of Levy (U and W) to provide the claimed method of

treatment because Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 27-34; and, Craig and Druzgala teach that thiazolidinediones are suitable for the treatment diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (V) in view of Levy et al. (U).

Applicant's claimed invention was set forth above. Applicant further claims the method according to Claim 2, wherein said powder is encapsulated.

The teachings of Takahashi were set forth above. Takahashi teaches the claim-designated methods except for wherein the powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Takahashi by administering the reference powdered extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition in an encapsulated form was conventional, as evidenced by the teachings of Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Takahashi by administering the reference powdered extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because Levy teaches that the oral administration of *Dunaliella bardawil* provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form

for the oral administration of the referenced algal compositions to effect a result variable for the treatment of the claim-designated disease conditions, since at the time the invention was made Takahashi teaches that the oral administration of effective amounts of a powdered extract of *Dunaliella* had therapeutic effects for the claim-designated disease condition, and given that Levy teaches that the encapsulation of a powdered extract of the claim-designated algal extract has therapeutic beneficial effects.

According, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 2 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (V) and Levy et al. (U)in view of Beck (A), Criere et al. (O), Clark et al. (C) and Heyman et al. (D).

Applicant's claimed invention of Claims 2 and 16-18 was set forth above. Applicant further claims a method according to claim 1, wherein said crude *Dunaliella* powder is administered together with one or more activators of nuclear receptors. Applicant further claims the method of claim 3, wherein the activators of nuclear receptors are peroxisome proliferator-activated receptor α or γ (PPARα or PPARγ) agonists. Applicant further claims the method according to claim 4, wherein the PPARα or PPARγ agonists are selected from fibrates and thiazolidinediones. Applicant further claims the method according to Claim 5, wherein the fibrates are selected from clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and gemfibrozil. Applicant

further claims the method according to Claim 5, wherein the thiazolidinediones are selected from AVANDIA™, troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone and rosiglitazone.

The combined teachings of Takahashi and Levy were set forth above. The combined teachings of Takahashi and Levy teach the claimed invention except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Takahashi and Levy to provide the claimed method of treatment because at the time the invention was made fibrates and thiazolidinediones were known in the art for their beneficial effect for treating the claim-designated disease conditions. Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceride-ciaias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of a thiazolidinedione, *e.g.,* troglitazone, BRL 49653 , pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation

of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Takahashi and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, *i.e.,* a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itoh et al. (X) in view of Takahashi et al. (V) and Levy et al. (U).

Applicant's claimed invention was set forth above.

Itoh teaches a method for reducing triglycerides and cholesterol levels in the plasma of hyperlipidemic rats comprising administrating to the subject an effective amount of an extract obtained from *Dunaliella bardawil.* Itoh teaches, "*Dunaliella* β-carotene lowered the plasma total cholesterol (TC), triglycerides (TG), LDL-cholesterol (LDL), phospholipids (PL), and free cholesterol (FC) levels of rats in both steps of lipid formation and excretion phase. Anti-lipididemic effect of *Dunaliella* β-carotene in lipid formation (TC, TG, PL, and FC) was remarkably higher than that in lipid excretion and depended on the dose of *Dunaliella* β-carotene."

The teachings of Itoh were set forth above. Itoh does not teach a method for reducing triglycerides comprising administering the claim-designated algal extract in the form of a crude powder and wherein the crude powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Itoh by administering the reference powdered extract of

Dunaliella bardawil in an encapsulated powdered form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition as a powder and as a powder in an encapsulated form was conventional, as evidenced by the teachings of Takahashi and Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Itoh by administering the reference powder extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because Takahashi teaches that the administration of an effective amount of a powder extract of *Dunaliella bardawil* to hypercholesterolemic mice significantly decreased the levels of plasma total cholesterol and LDL-cholesterol and Levy teaches that the oral administration of *Dunaliella bardawil* provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form for the oral administration of the reference algal compositions to effect a result variable for the treatment of the claim-designated disease conditions, since at the time the invention was made Takahashi teaches that the oral administration of a powder extract of *Dunaliella bardawil* provides an anti-hypercholesterolemic beneficial functional effect and Levy teaches that the encapsulation of a powder extract of the claim-designated algal extract has therapeutic beneficial effects.

According, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 2 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itoh et al. (X), Takahashi et al. (V) and Levy et al. (U) in view of Beck (A), Criere et al. (O), Clark et al. (C) and Heyman et al. (D).

The combined teachings of Itoh, Takahashi and Levy were set forth above. The combined teachings of Itoh, Takahashi and Levy teach the claimed invention except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Itoh, Takahashi and Levy to provide the claimed method of treatment because at the time the invention was made fibrates and thiazolidinediones were known in the art for their beneficial effect for treating the claim-designated disease conditions. Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceride-ciaias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of a

thiazolidinedione, *e.g.,* troglitazone, BRL 49653 , pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Itoh, Takahashi and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPARγ agonist, *i.e.,* a thiazolidinedione, achieves synergistic action of the RXR/ PPARγ heterodimers so as to enhance adipogenic and antidiabetic effects of PPARγ.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman,* 1943 C.D. 518. Applicants invention may be predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the

components embraced by the claims, which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above-cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele C. Flood whose telephone number is (571) 272-0964. The examiner can normally be reached on 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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